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biology, Vol. 38(12), pp. 1911-1922, Dec 1993

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(54) Abstract Title
In-vivo photoacoustic measurement

(57) A biological parameter is measured by directing laser pulses from a light guide (10) into a body part consisting of soft tissue, such as the tip of a finger (12), to produce a photo-acoustic interaction. Sound waves (14) generated by absorption of the optical beam are detected by a transducer (16). The detector and optical beam guide are housed in a body-part shaped sensor head device (figures 2 to 16), and are preferably not co-linear with one another. Analysis of the transducer output enables calculation of the desired parameter, e.g. blood glucose concentration.
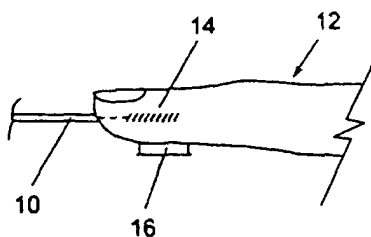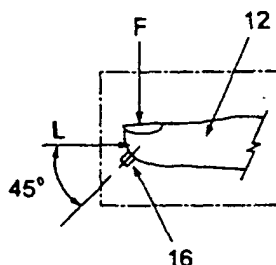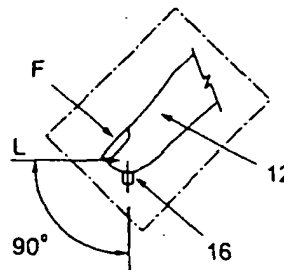
Fig. 1a

Fig. 1b

Fig. 1c

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Fig. 1a

Fig. 1b

Fig. 1c

Fig. 2

Fig. 4

Fig. 3

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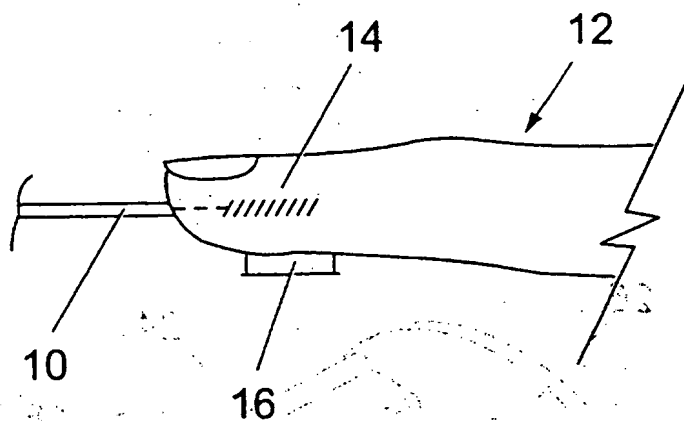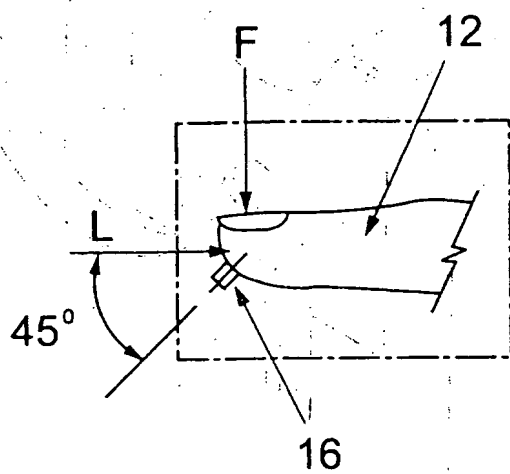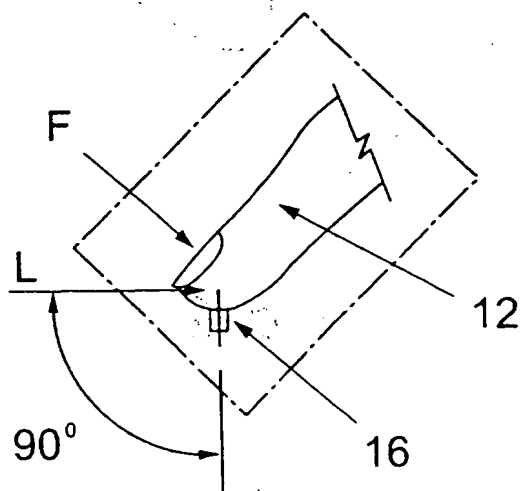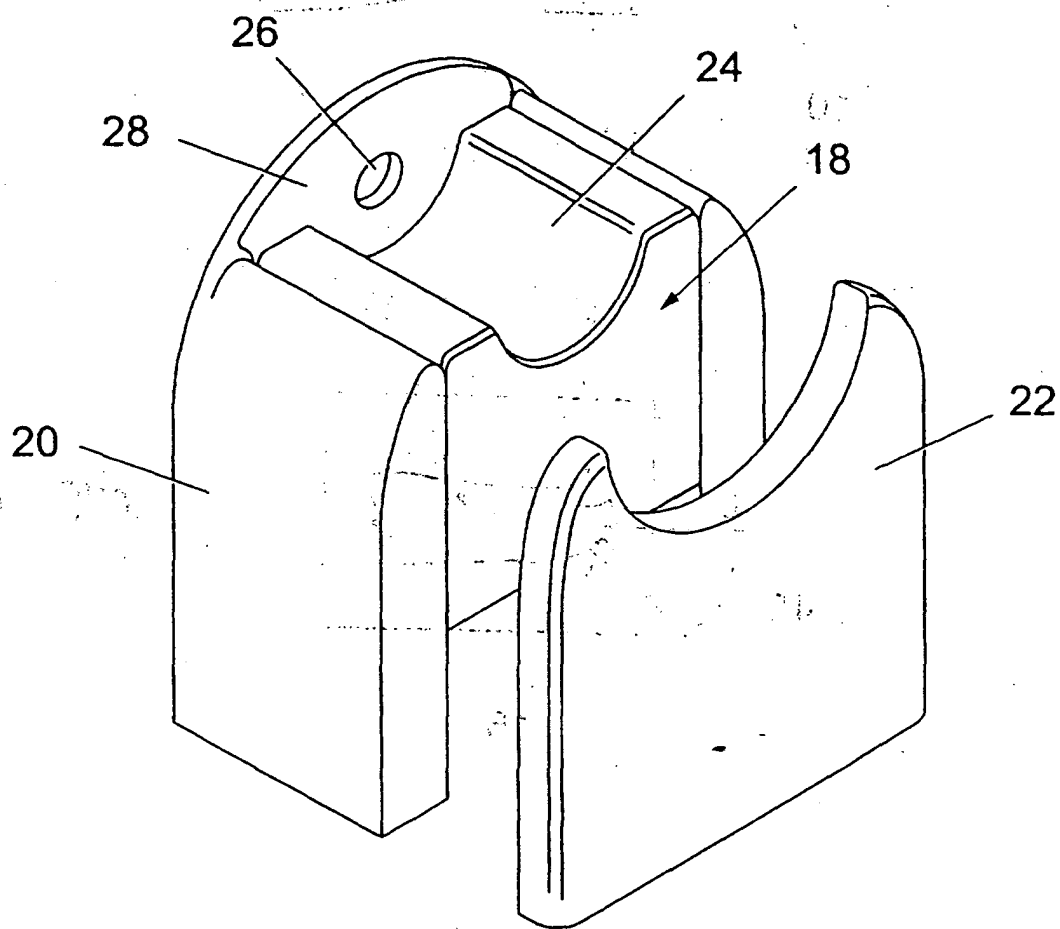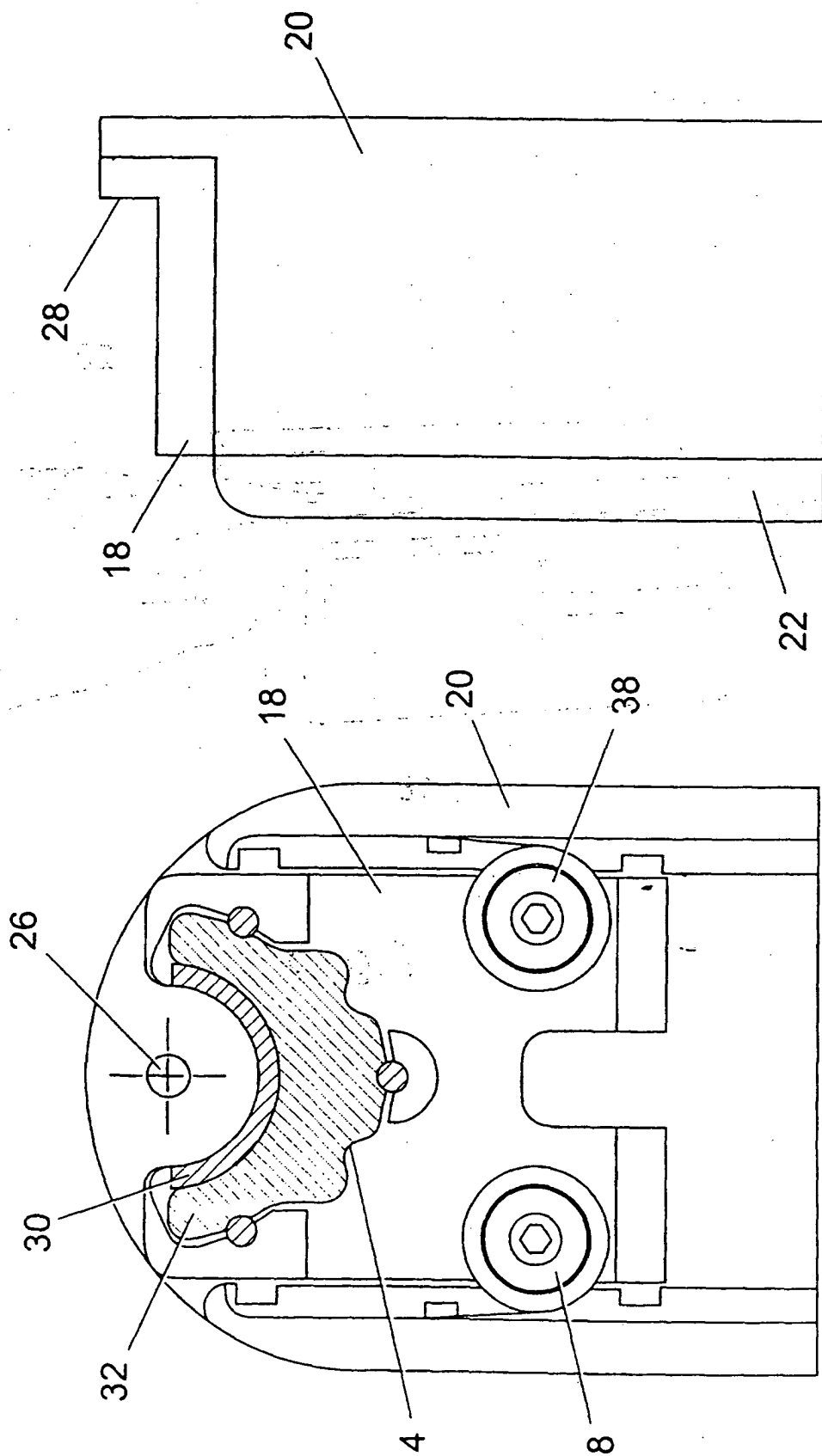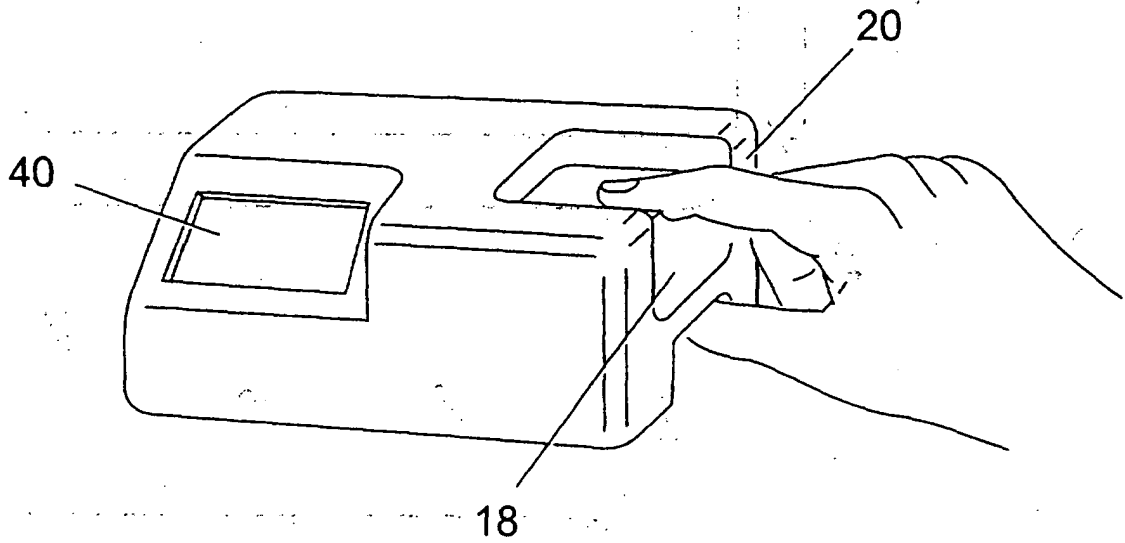
Fig. 5

Fig. 6

Fig. 7

Fig. 8a

Fig. 8b

76

Fig. 10

Fig. 11

Fig. 12

111

109

108

106

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107

105

Fig. 13

204

202

200

108

206

Fig. 13a

120 —— | 120 mg/dl | —— 121

119

118

117

115

116

114

113 112

Fig. 14

Fig. 15

128

130

129
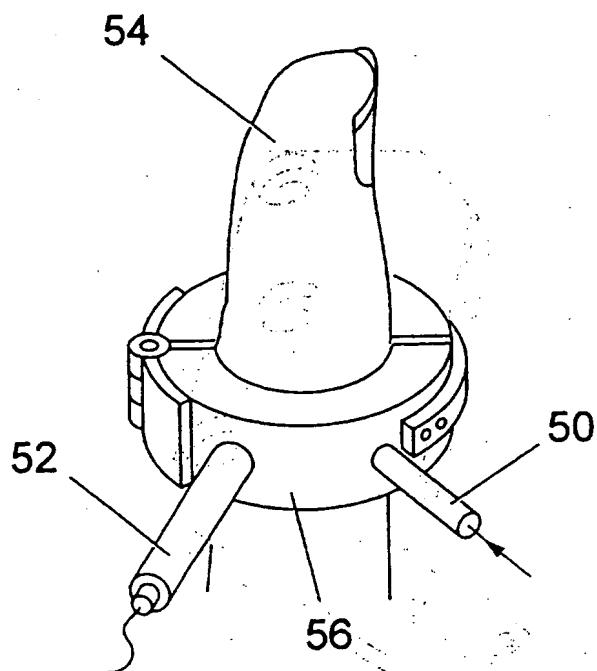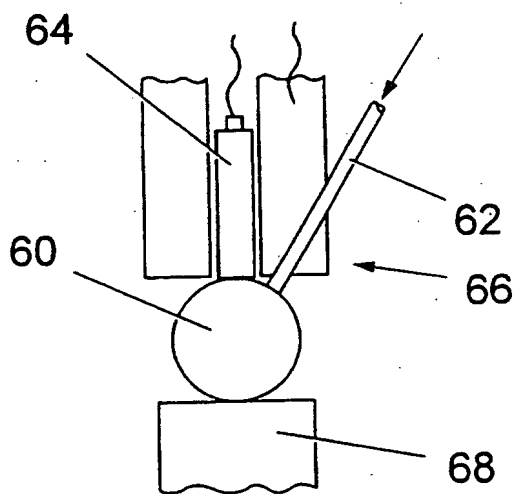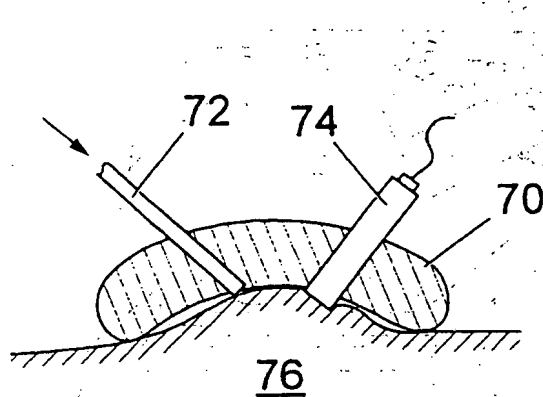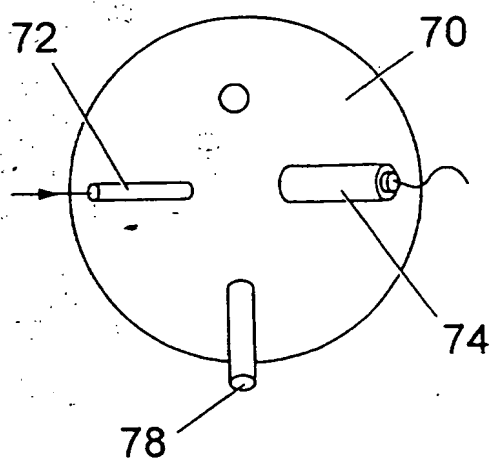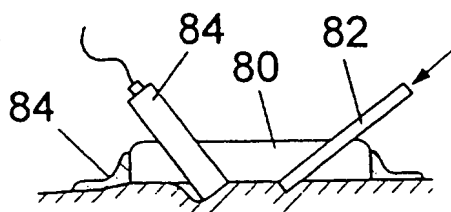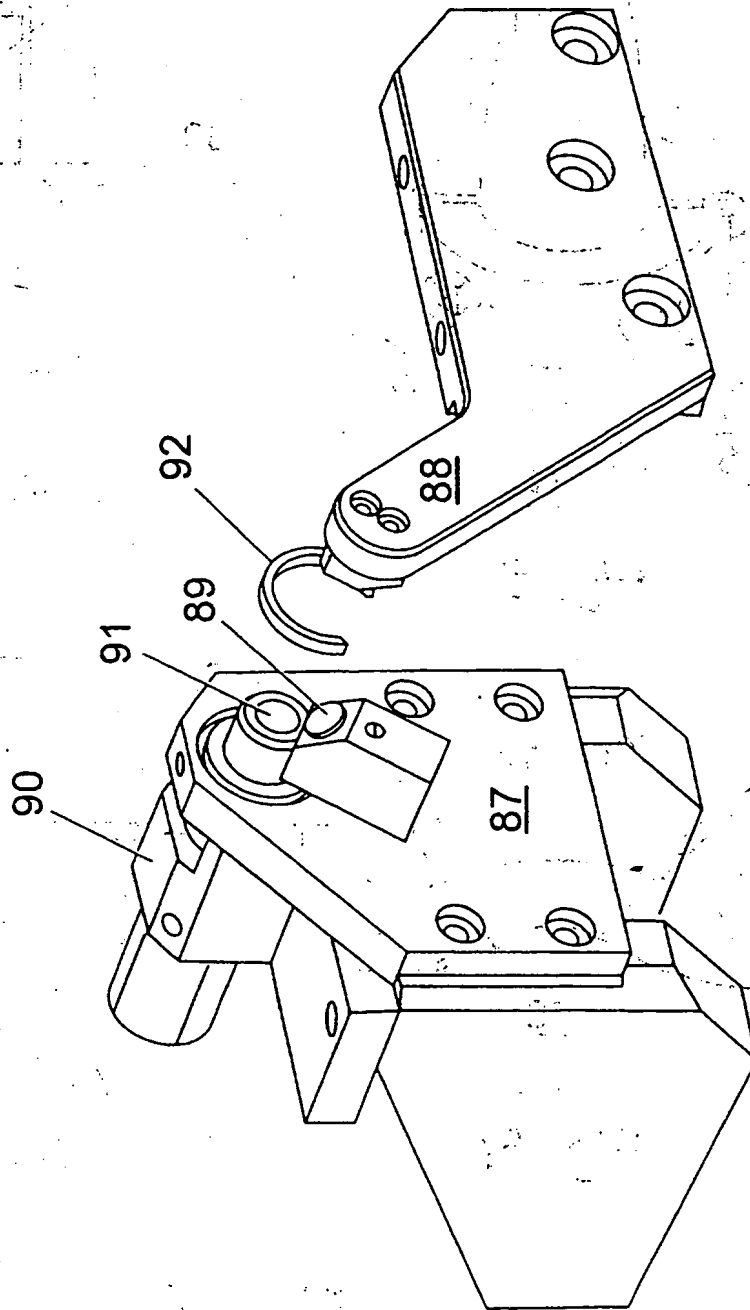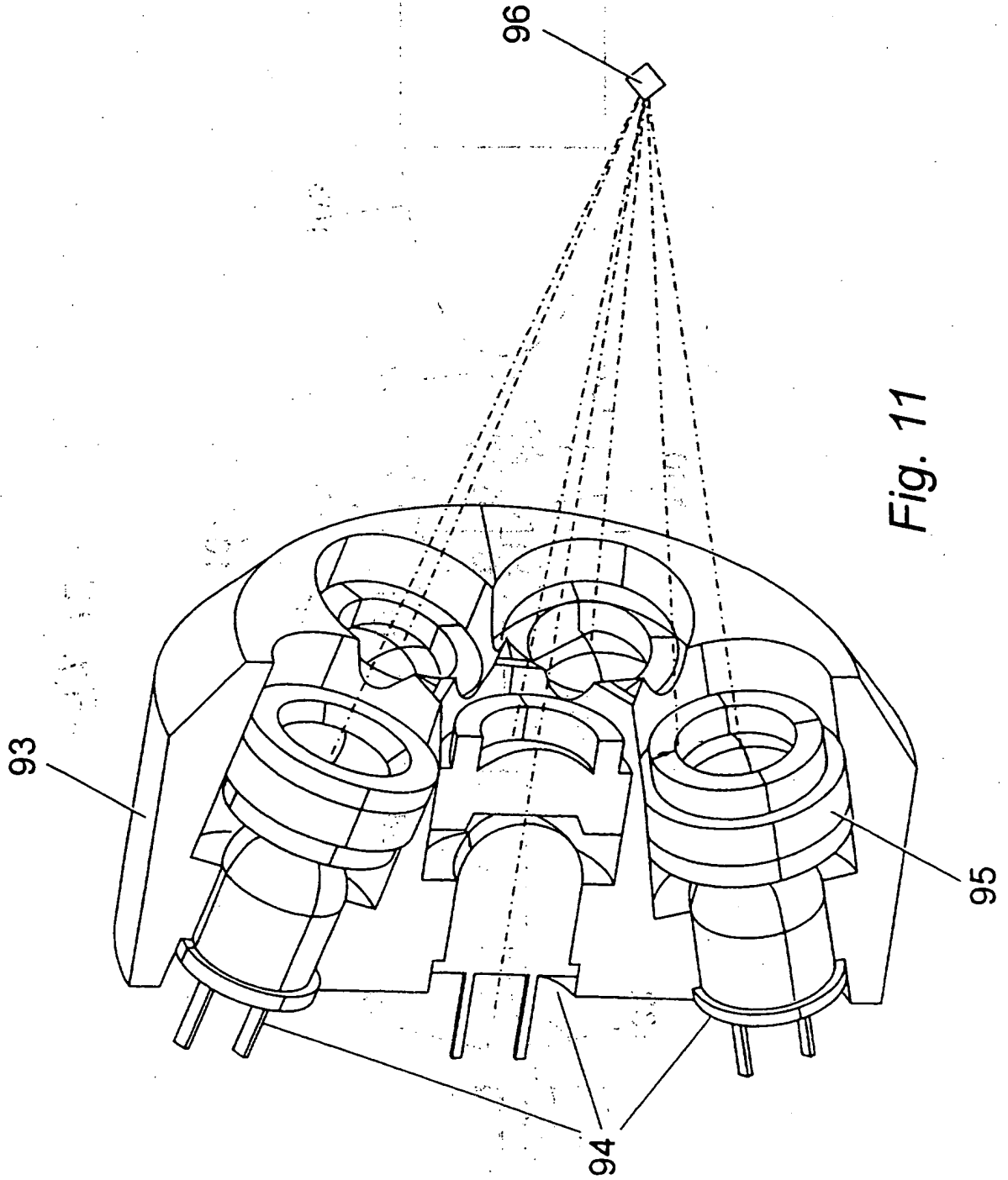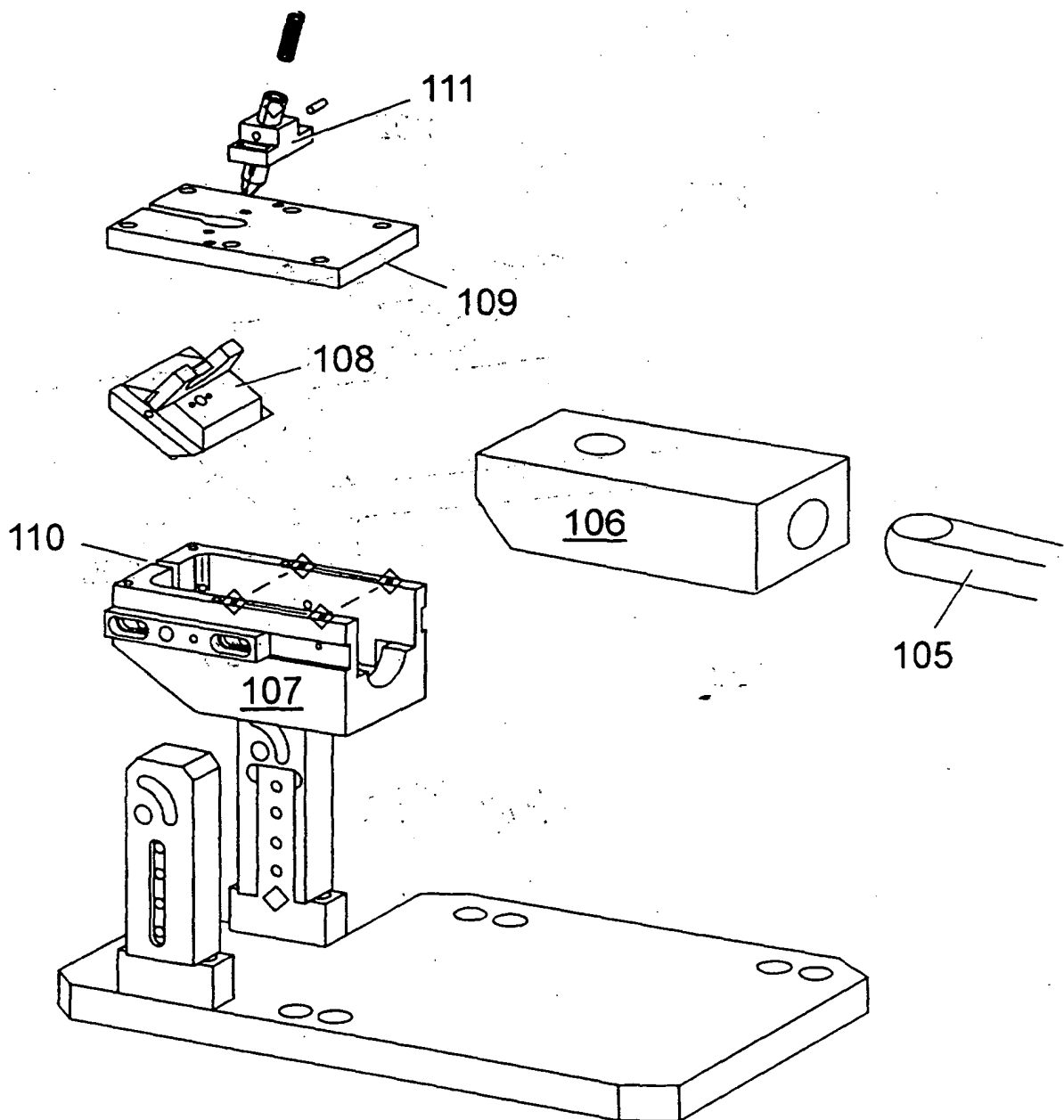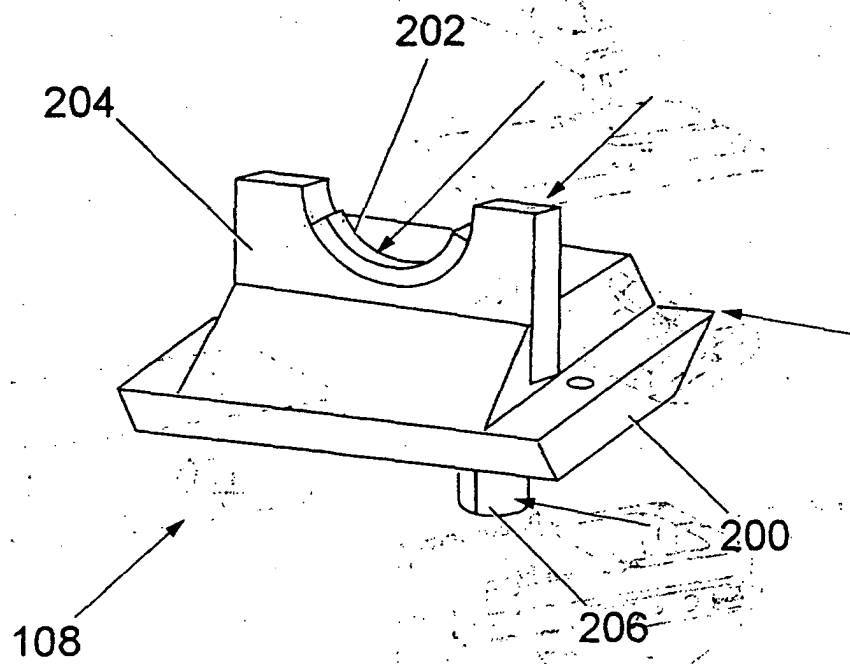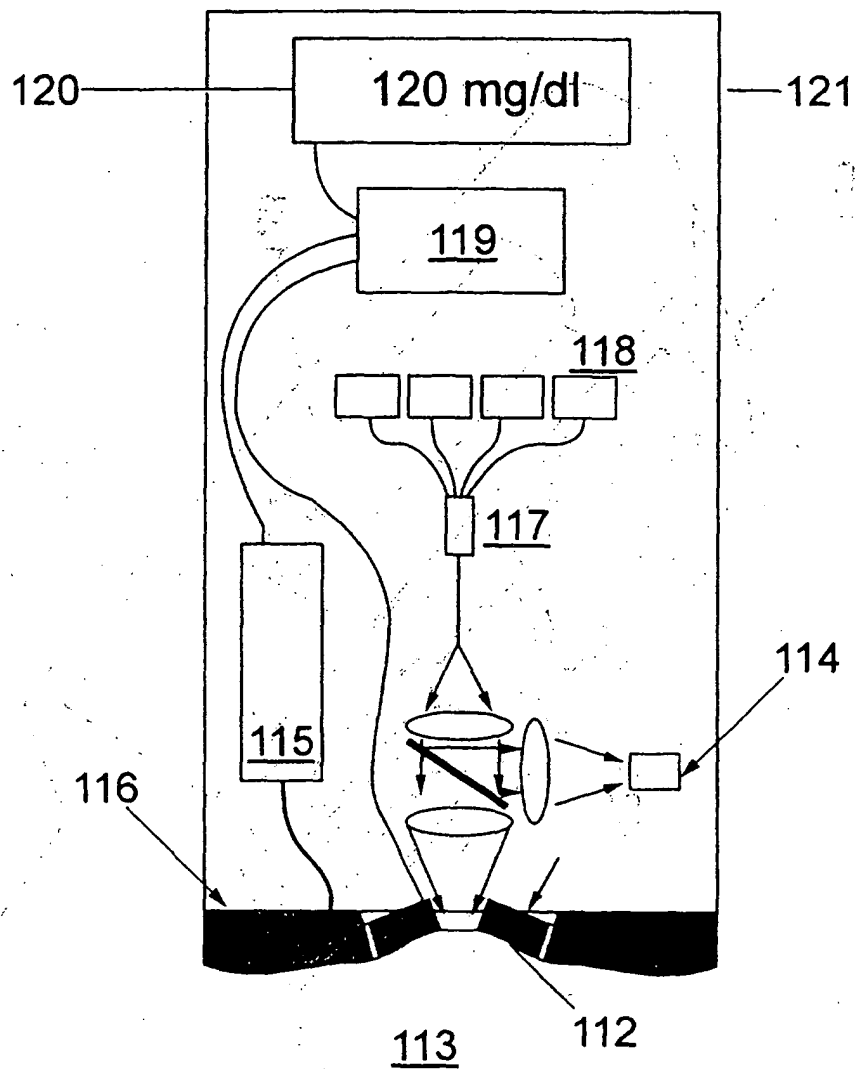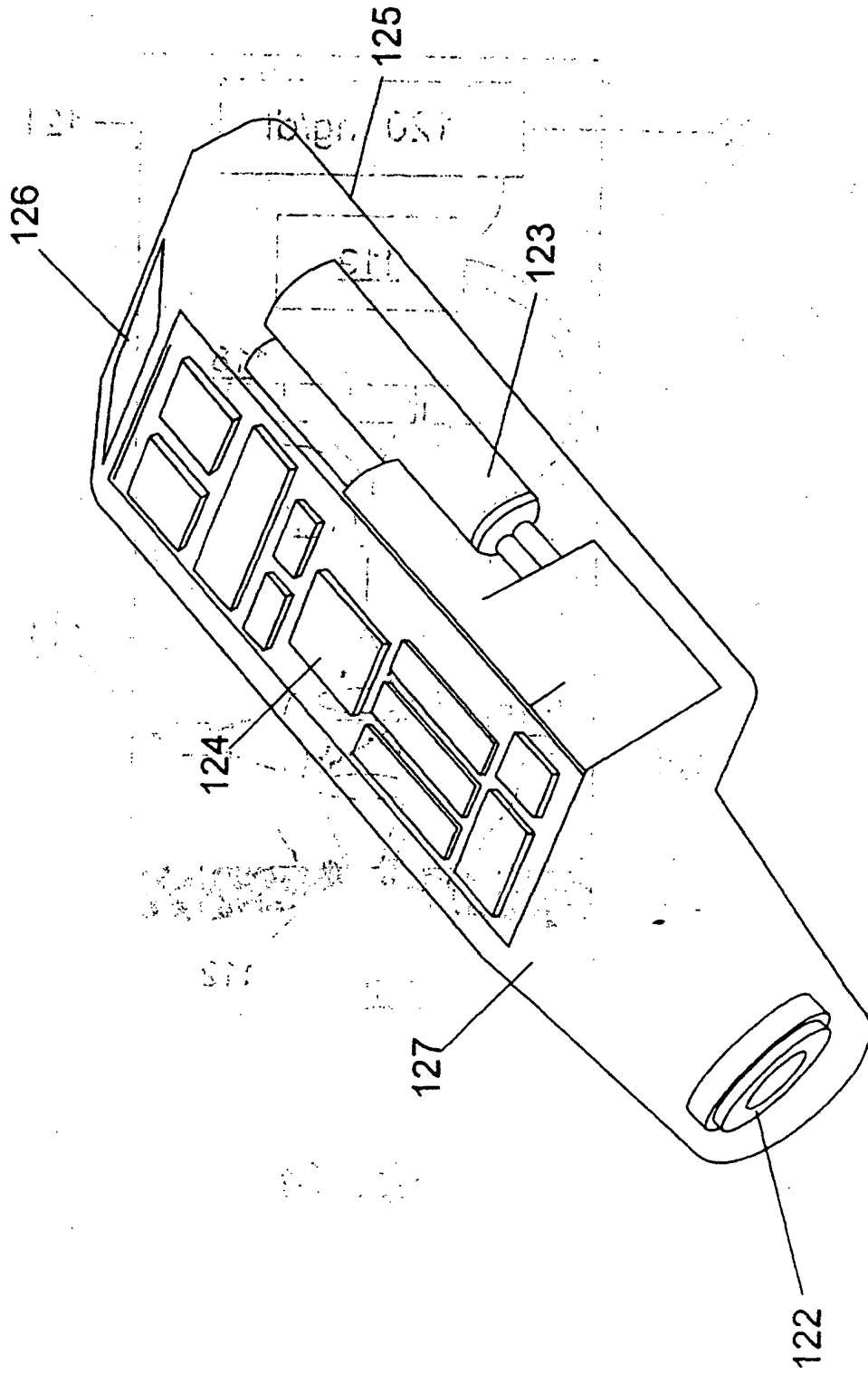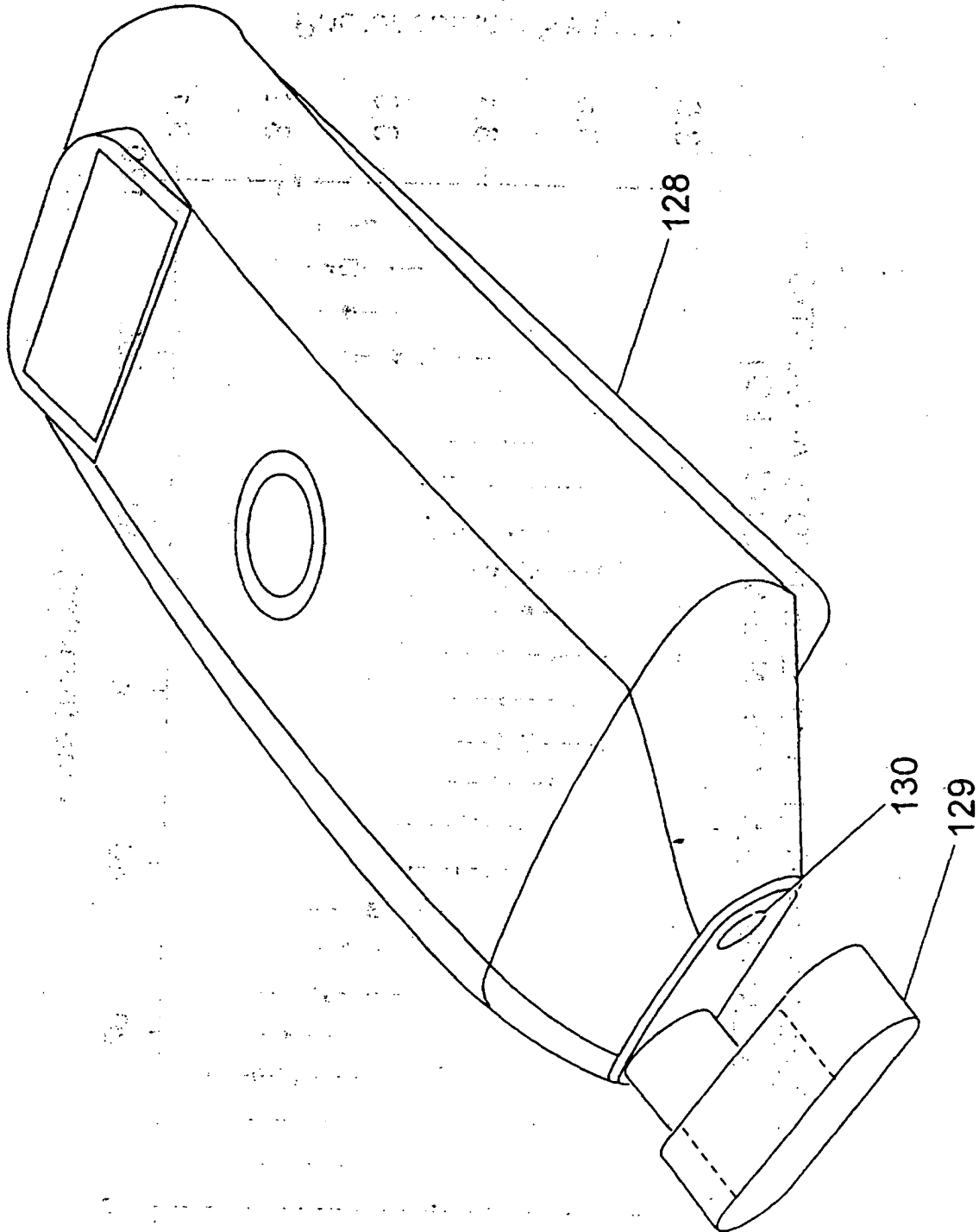
Fig. 16

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC
MEASUREMENT FOR NORMAL SUBJECT

Photoacoustic Responce
(volts)

Clinical Blood Glucose
Concentration (mmol/l)

Time (minutes)

Fig. 17

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC
MEASUREMENT FOR TYPE 1 DIABETIC
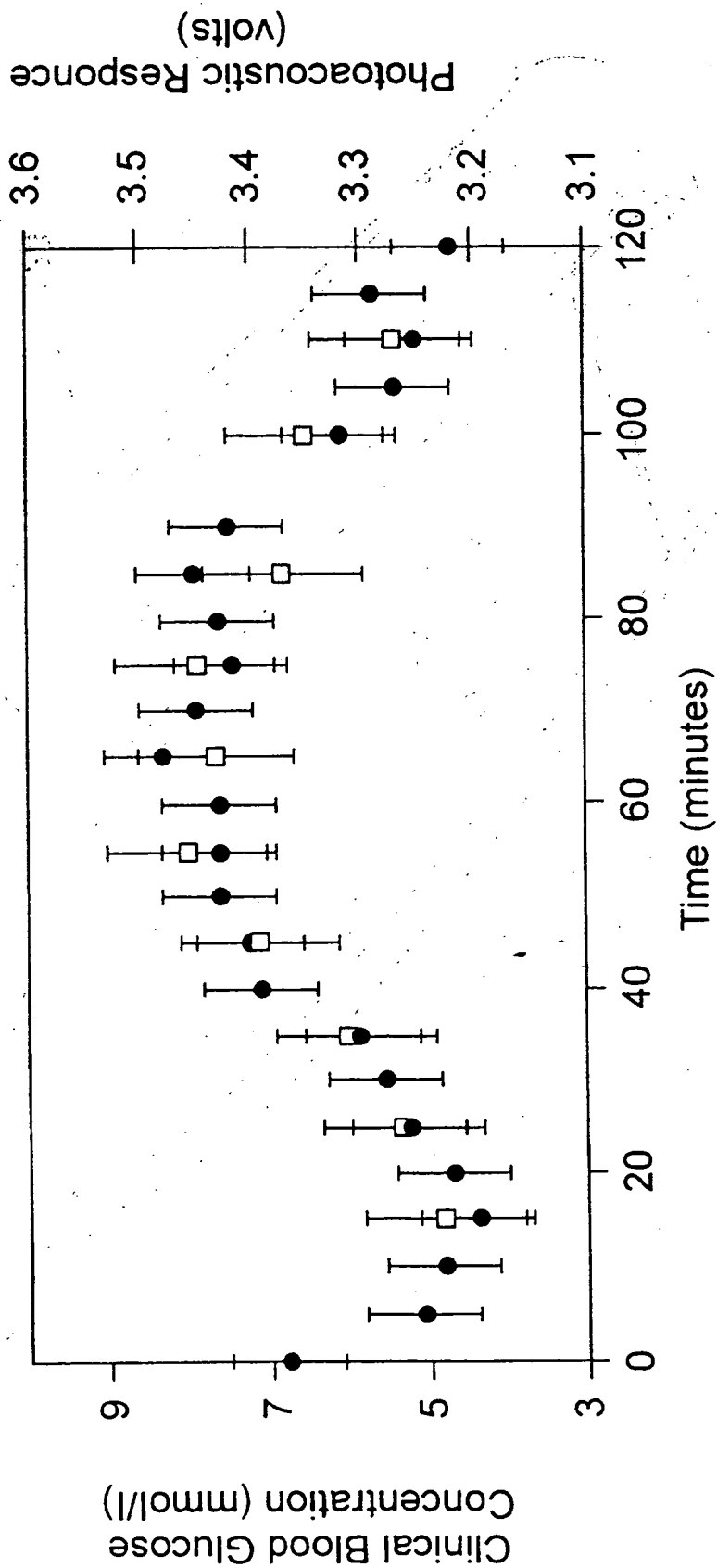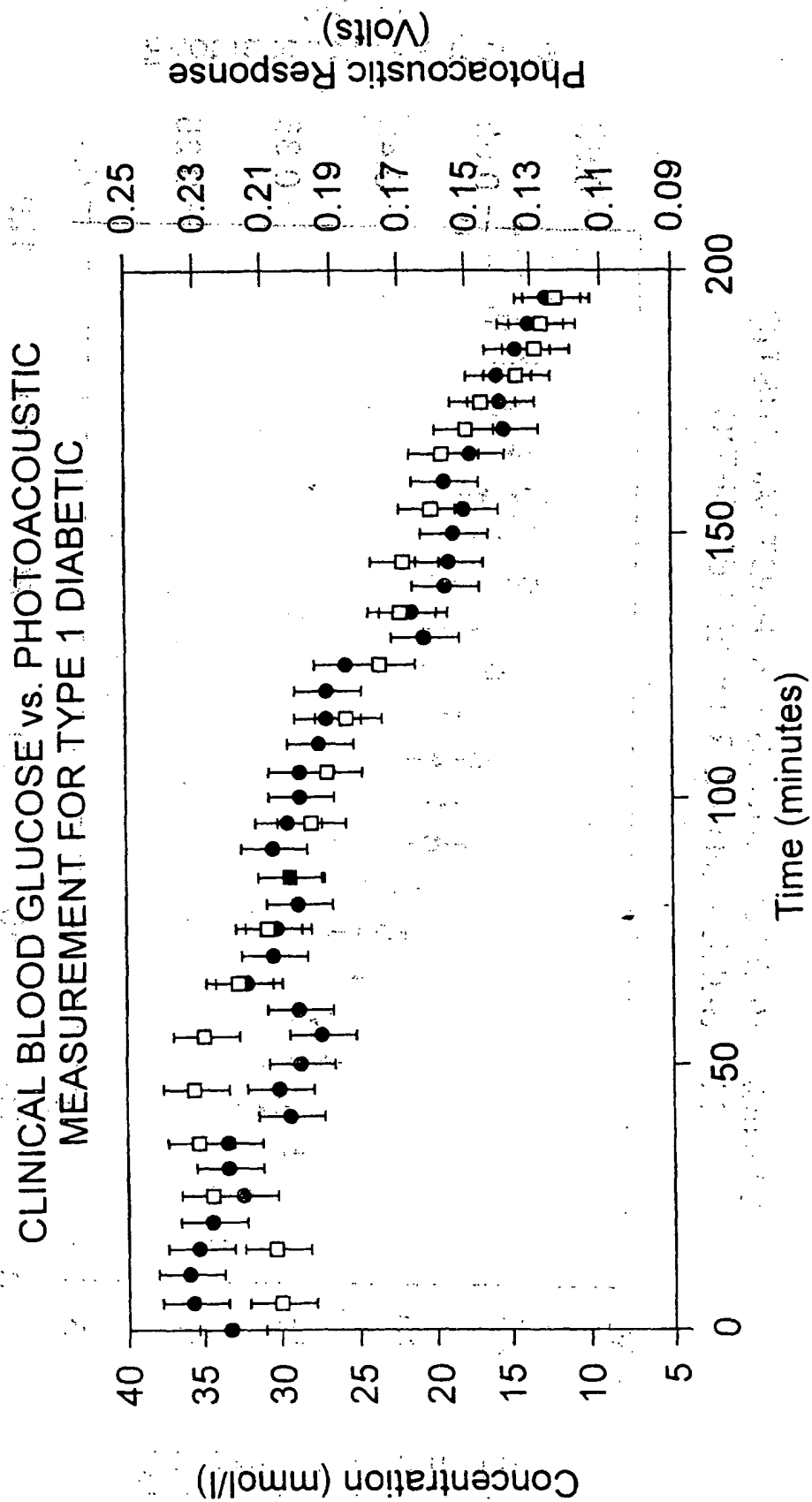
Fig. 18

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC
MEASUREMENT FOR TYPE 2 DIABETIC

Clinical blood glucose
Concentration (mmol/l)

Photoacoustic Response
(volts)

Time (minutes)
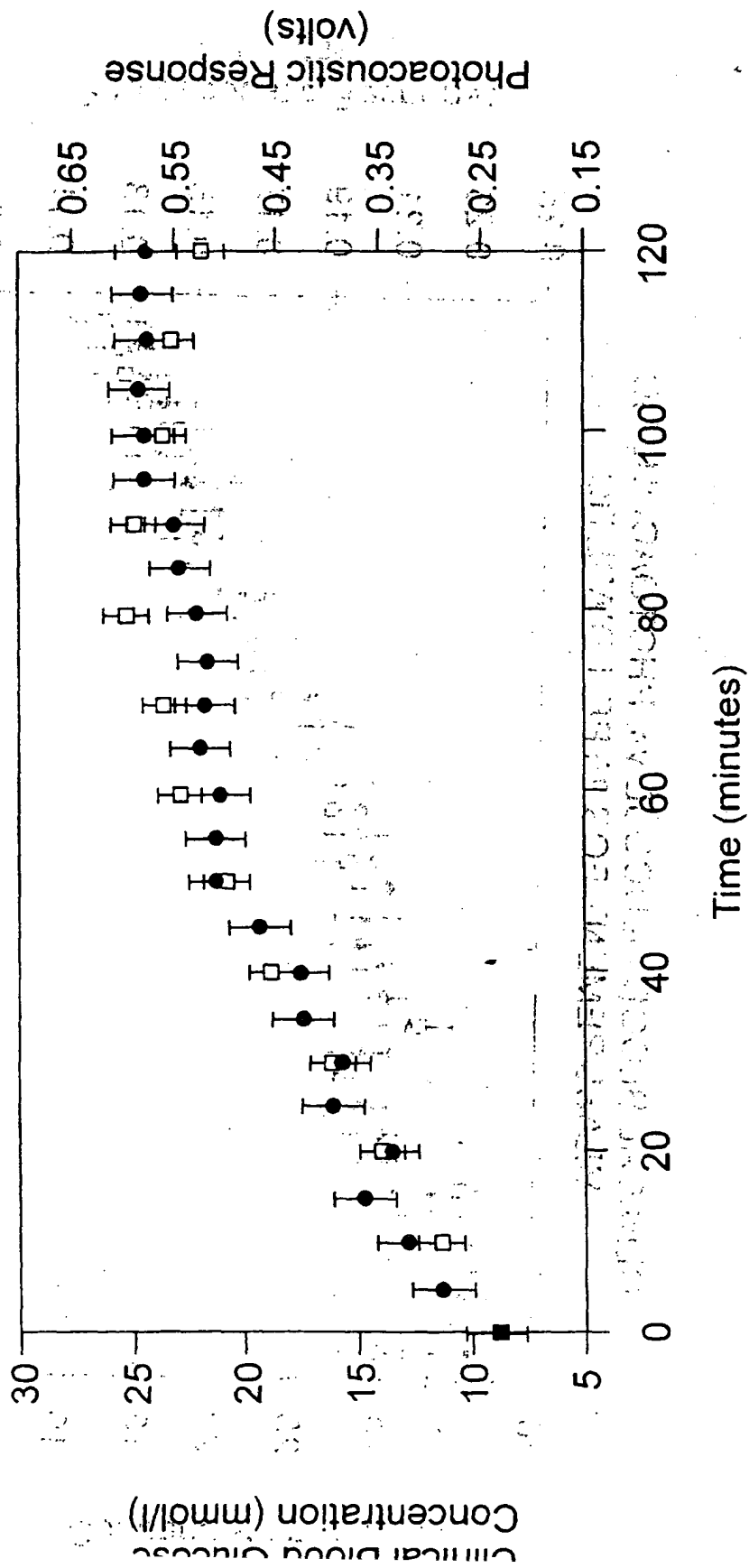
Fig. 19

Biological Measurement System

This invention relates to apparatus for use in non-
invasive in vivo monitoring of physiological substances
such as blood and the like.

One particular, but not exclusive, application of the
present invention is in the monitoring of blood
glucose, for example in the management of diabetes
mellitus. It is accepted that the management of
diabetes can be much improved by routine monitoring of
blood glucose concentration and clinicians suggest that
monitoring as often as four times per day is desirable.

The monitoring technique currently available for use by
patients involves using a spring loaded lancet to stab
the finger to obtain a blood sample which is
transferred to a glucose test strip. The concentration
is derived either by reading the test strip with a
reflectance meter or by visual comparison of colour
change against a colour scale. Many diabetics find the
testing onerous as the technique is painful,
inconvenient, messy, potentially embarrassing and
offers a site for the transmittance and acceptance of
infection.

1   Techniques have also been developed for non invasive

2   measurement using transmittance or reflectance

3   spectroscopy. However the required instruments are

4   expensive and it is difficult to obtain accurate and

5   repeatable measurements.

6

7   There are also known various types of in vivo chemical

8   sensors. These rely on implanting minimally invasive

9   sensors under the skin surface, but such sensors have

10   poor long term reproducibility and bio-compatibility

11   problems.

12

13   There is therefore a need for improved means for

14   routine monitoring of blood glucose in a manner which

15   is simple and straightforward to use.

16

17   The present invention makes use of photoacoustic

18   techniques. The fundamentals of photoacoustic

19   techniques are well known per se. A pulse of light,

20   typically laser light, is applied to a substance

21   containing an analyte of interest in solution or

22   dispersion, the wavelength of the applied light being

23   chosen to interact with the analyte. Absorption of the

24   light energy by the analyte gives rise to microscopic

25   localised heating which generates an acoustic wave

26   which can be detected by an acoustic sensor. These

27   techniques have been used to measure physiological

28   parameters in vitro.

29

30   US Patents 5348002 and 5348003 (Caro) propose the use

31   of photoacoustics in combination with photoabsorption

32   for the measurement of blood components in vivo.

33   However, the arrangement proposed by Caro has not been

34   demonstrated as a workable system and may suffer from

35   interference to a degree which would preclude useful

36   acoustic signals, and since they would also suffer from

1 interference and resonance effects from hard structures

2 such as bone.

3

4 It has also been proposed by Poulet and Chambron in

5 <u>Medical and Biological Engineering and Computing</u>,

6 November 1985, Page 585 to use a photoacoustic

7 spectrometer in a cell arrangement to measure

8 characteristics of cutaneous tissue, but the apparatus

9 described would not be suitable for measuring blood

10 analytes.

11

12 Published European Patent Application 0282234A1

13 (Dowling) proposes the use of photoacoustic

14 spectroscopy for the measurement of blood analytes such

15 as blood glucose. This disclosure however does not

16 show or suggest any means which would permit the

17 required degree of coupling to body tissues for use in

18 vivo.

19

20 Accordingly, the present invention provides a sensor

21 head for use in photoacoustic in vivo measurement,

22 comprising a housing shaped to engage a selected body

23 part, light transmission means terminating in said

24 housing so as to transmit light energy from a light

25 source to enter the body part along a beam axis, and

26 acoustic transducer means mounted in the housing to

27 receive acoustic waves generated by photoacoustic

28 interaction within the body part, the acoustic

29 transducer means being disposed in the housing to

30 receive said acoustic wave in a direction of high

31 acoustic energy.

32

33 The expression "direction of high acoustic energy" is

34 used herein to denote a direction other than the

35 forward direction of the light beam. Preferably, the

36 transducer means is disposed so as to intercept

1   acoustic energy propagating at right angles to the

2   optical beam axis, or at an angle to the optical beam

3   axis which may be down to about 20°, typically about

4   -45°.

5

6   An exact measure of the angle of high acoustic energy

7   can be worked out but is dependent upon the specific

8   geometry of the light source, the properties of the

9   tissue and the absorption coefficient of the tissue.

10   One model for understanding the propagation of the

11   acoustic energy in any homogenous media was developed

12   by Huyghens and is called the principle of

13   superposition. In this model each volume element that

14   is illuminated by the light generates an acoustic

15   pressure wave that radiates outward in a spherical

16   manor. The magnitude of the pressure wave at each

17   volume element depends on the intensity of the optical

18   beam at that location, the absorption coefficient of

19   the material at that location, the wavelength of light

20   and on several other physical properties of the

21   material such as the speed of sound and the specific

22   heat. The signal measured at the detector is just the

23   superposition of all pressure waves from all points

24   that are illuminated by the source light. An

25   analytical solution for the pressure wave has been

26   worked out for a few cases in aqueous material. The

27   analytical case that best matches the in-vivo

28   measurements is that of a cylindrical optical beam

29   propagating in a weekly absorbing material. In this

30   case the direction of highest acoustic energy is

31   perpendicular to the optical axis. The base detector

32   location is with the plane of the detector

33   perpendicular to the acoustic energy, or parallel to

34   the optical axis. This is because the acoustic

35   detector has the highest sensitivity when the acoustic

36   energy strikes the detector perpendicular to the plane

1   of the detector. This analytical model is not

2   completely accurate for the in-vivo measurement case

3   because of scattering of the tissue and because the

4   tissue absorbs more than the model predicts. These

5   differences indicate that a different position for the

6   detector will be optimal. A detailed numeric model is

7   required to determine the best detector location and is

8   dependent upon the beam properties (focused to a point,

9   colligated, etc.); body site (finger, earlobe, arm

10 etc.) and wavelength. One skilled in the art can

11 readily develop an appropriate mode. However, suitable

12 locations for a detector will generally be at an angle

13 to the optical axis. Angles between 40 and 90 degrees

14 should be suitable.

15

16 In one preferred arrangement, the acoustic transducer

17 means is arranged parallel to the optical beam axis.

18 This arrangement is particularly suitable for use where

19 the selected body part is the distal portion of a

20 finger, in which case the housing may include a

21 generally half-cylindrical depression in which the

22 finger may be placed with the light transmission means

23 aimed at the end of the finger.

24

25 Preferably, the acoustic transducer means comprises a

26 piezoelectric transducer which most preferably is of a

27 semi-cylindrical shape. This transducer may be

28 provided with a backing of lead or other dense

29 material, and the backing may have a rear surface

30 shaped to minimise internal acoustic reflection.

31

32 Alternative transducer means include a capacitor-type

33 detector, which is preferably small and disk-shaped; an

34 integrated semiconductor pressure sensor; and an

35 optical pressure sensor, for example based on an

36 optical fibre.

1   In an alternative arrangement, the plane of the

2   transducer may be arranged to be perpendicular to the

3   optical axis to detect the acoustic wave which is

4   propagating in a direction opposite to the direction of

5   the light beam. For example, the acoustic transducer

6   means may be part-spherical with an aperture to allow

7   access for the light beam. This may be particularly

8   suitable for engagement with a body part other than the

9   finger, for example the back of the arm.

10

11   The generation of a surface acoustic wave is an

12   inherent aspect of the in vivo pulsed photoacoustic

13   generation in tissue and may be used to characterize

14   tissue properties such as density. A surface wave

15   detector may be provided in the sensing head assembly.

16

17   Preferably means are provided for ensuring a consistent

18   contact pressure between the selected body part and the

19   acoustic transducer means. In the case where the

20   selected part is the distal portion of the finger, said

21   means may be provided by mounting the portion of the

22   housing engaged by the finger in a resiliently biased

23   fashion against the remainder of the housing, and

24   providing means to ensure that measurement is effected

25   when the predetermined force or pressure is applied by

26   the subject against the resilient bias. In the case

27   where the selected part is the earlobe, said means may

28   be provided by placing the ear between two plates and

29   applying pressure to the ear with springs or weights or

30   other force method. The two plates holding the ear may

31   contain a removable insert. The two plates may be flat

32   or may be of another shape to optimally position the

33   detector with respect to the beam axis.

34

35   In addition, the present invention provides a sensor

36   head for use in photoacoustic in-vivo measurements,

comprising a housing shaped to receive a removable
insert, a removable insert that engages a selected body
part, the insert being fitted to an individual,
allowing for a range of sizes of body parts to be used,
and further comprising light transmission means
terminating in or near said removable insert so as to
transmit light energy from a light source or sources to
enter the body part along a beam axis, and an acoustic
transducer means mounted in the housing or in the
removable insert to receive acoustic waves generated by
photoacoustic interaction within the body part to
receive said acoustic waves in a direction of high
acoustic energy.

From another aspect the present invention provides an
in vivo measuring system comprising a sensor head as
hereinbefore defined in combination with a light source
coupled with the light transmission means, and signal
processing means connected to receive the output of the
acoustic transducer means and to derive therefrom a
measurement of a selected physiological parameter.

Preferably, the light transmission means is a fiber
distribution system where each light source is
connected to an individual fiber and when multiple
light sources are used the multiple fibres are joined
by some standard fiber combining method, such as a
wavelength division multiplexer or a fiber coupler.
The fiber that comes from the light source, or contains
the combined light for a multiple source system, is
then terminated in proximity to the body part being
measured. The fiber could be in contact with the body
part or alternatively standard optics, such as lenses,
beamsplitters and such, could be employed to convey the
light from the end of the fiber to the body part. A
reference detector or several reference detectors and

1   beamsplitters can be added to the optical distribution

2   system to determine the energy of the light entering

3   the body part.

4

5   Alternatively, the optical distribution system may

6   contain mechanical holders, lenses and such to convey

7   the light from the source, or sources, to a location in

8   proximity to the body part being measured. A reference

9   detector or several reference detectors and

10   beamsplitters can be added to the optical distribution

11   system to determine the energy of the light entering

12   the body part.

13

14   The acoustic signal from the detector contains

15   information in both time and frequency, and there may

16   be information from several sources. The processing

17   means is preferably a multi-dimensional processing

18   method, such as Classical Least Squares (CLS) or

19   Partial Least Squares (PLS). Alternatively the

20   processing method may be more flexible, such as a

21   Neural Network. In addition to these methods the

22   signals may be analysed for their frequency content

23   using such techniques as Fourier Analysis or Frequency

24   Filtering In addition techniques may be employed that

25   use time information such as the time delay from source

26   trigger. Techniques that combine both frequency and

27   time information may be employed, such as Wavelet

28   analysis.

29

30   The light source is preferably a laser light source and

31   is most suitably a pulsed diode laser, but may utilise

32   a set of such lasers or utilise a tunable laser source.

33   In a particularly preferred form, suitable for use in

34   measuring blood glucose concentration, a laser diode is

35   used with a wave length in the range of approximately

36   600 nm to 10,000 nm and a pulse duration of the order

1 of 5 to 500 ns.

2

3 The delivery to the measurement site may be either

4 directly or by optical fibre with a suitable optical

5 element to focus the beam into the tissue.

6

7 Preferably means are provided for time multiplexing

8 multiple sources when multiple sources are used. Each

9 source is switched on, and it generates an optical

10 pulse, or a set of optical pulses. This pulse, or set

11 of pulses, generates an acoustic signal that is

12 detected by the detector. Each source is pulsed in

13 sequence until all sources have been used to generate

14 their own signal.

15

16 The measuring system may conveniently be in the form of

17 a self contained system including a power supply and a

18 readout, which may be carried on the person and used at

19 any convenient time.

20

21 It is also possible for such a self contained system to

22 incorporate, or to be provided with facilities for

23 connection to, a cellular telephone, two-way pager or

24 other communication device for routine transmission of

25 measurements taken to a central data collection point.

26

27 In addition the measuring system may have provision for

28 manipulating the body part under measurement and for

29 performing additional measurement of the tissue to get

30 other information about the state of the physiology of

31 the issue. It is well-known in the art that squeezing

32 a section of tissue to increase the pressure and then

33 releasing the pressure will cause changes in the total

34 blood volume in the measurement site. The present

35 invention may allow for this type of manipulation

36 including the squeezing of a body part, such as an

1   earlobe, and making photo acoustic measurements at

2   several different pressures. The present invention may

3   also allow for the measurement of the temperature of

4   the body site and to apply a correction to the

5   measurements based upon the temperature of the body

6   site.

7

8   Another type of physiological manipulation is body

9   temperature. It is known in the art that several

10   parameters involved in the detection of the photo

11   acoustic signal, such as the speed of sound, are

12   dependent upon the temperature of the medium the signal

13   is propagating through (the tissue). Also the

14   profusion of the blood in the small capillaries is

15   dependent upon the temperature of the tissue.

16   Additional information about the tissue can be obtained

17   if the photo acoustic measurement is made at several

18   temperatures, both higher and lower than ambient

19   temperature. This additional information is used to

20   better eliminate interferences to the determination of

21   the analyte under investigation. These are only two

22   examples of manipulating the body site and are not

23   intended to be an exhaustive list, and they can be used

24   in combination with other manipulation techniques.

25

26   The in-vivo measuring system may comprise a means for

27   storing calibration coefficients or operation

28   parameters or both calibration coefficients and

29   operational parameters, in order to calibrate the

30   instrument and to set critical operational parameters.

31

32   Another aspect of the present invention provides a

33   means for adjusting the calibration coefficients and

34   operational parameters to be specific to a particular

35   person and may be used to adjust for such things as

36   body part size, skin color, skin condition, amount of

1   body fat, efficiency of the detector and efficiency of

2   the source(s).

3

4   In addition the present invention may provide for

5   having the specific calibration coefficients and

6   operational parameters be contained in a storage site

7   located in the removable insert. This allows for the

8   system to be both mechanically and operationally

9   configured to a particular individual. Additionally

10   the invention may allow for the calibration

11   coefficients and operational parameters to be stored in

12   two locations, one in the non-removable housing and one

13   in the removable insert with some of the coefficients

14   and parameters stored in each location. This allows

15   for reader system coefficients to be stored in the

16   reader and coefficients specific to an individual to be

17   stored in the removable insert for that person,

18   enabling many people to use the same reader.

19

20   Another aspect of the present invention provides means

21   for connecting the non-invasive measuring system to an

22   invasive measuring system for the purpose of

23   calibrating or adjusting the operational parameters of

24   the non-invasive measuring system. Such connection may

25   be accomplished, but is not limited to, communication

26   by a wire, IR link or radio waves.

27

28   Another aspect of the present invention provides a

29   method for removing instrument drift from the

30   measurement comprising the steps of:

31

32   1.   Placing a standard in the reader in place of the

33   body part.

34

35   2.   Measuring the signal from the standard for each

36   wavelength and storing the values in the

1   calibration storage location.

2

3   3.   Before making a measurement of a body part,

4   placing the calibration standard in the reader.

5

6   4.   Measuring the signal from the standard for each

7   source.

8

9   5.   Comparing the just measured standard values to the

10   stored calibration values.

11

12   6.   Calculating correction factors for each source

13   wavelength.

14

15   7.   Removing the standard and placing the body part in

16   the reader.

17

18   8.   Measuring the signal from the body part for each

19   source.

20

21   9.   Adjusting the measured values using the calculated

22   correction factors.

23

24   In addition to the signal correction factors a

25   correction factor can be calculated for the instrument

26   temperature. This can be applied to each signal with a

27   different correction coefficient.

28

29   The invention further provides a method of measuring a

30   biological parameter in a subject, the method

31   comprising the steps of:

32

33   directing one or more pulses of optical energy

34   from the exterior into the tissue of a subject

35   along a beam axis, the optical energy having a

36   wavelength selected to be absorbed by tissue

1   components of interest, thereby to produce a

2   photoacoustic interaction;

3

4   detecting acoustic energy resulting from said

5   photoacoustic reaction by means of a transducer

6   positioned to intercept acoustic energy

7   propagating in a direction other than the forward

8   direction of said beam axis; and

9

10   deriving from said detected acoustic energy a

11   measure of the parameter of interest; and a

12   corresponding apparatus.

13

14

15 Embodiments of the invention will now be described, by

16 way of example only, with reference to the accompanying

17 drawings in which:-

18

19   Figs. 1A,1B and 1C are side views illustrating the

20   principle of operation of one embodiment of the

21   present invention;

22

23   Fig. 2 is a schematic perspective view showing a

24   sensor head for use in carrying out the

25   measurement illustrated in Fig. 1;

26

27   Fig 3. is a cross section view of the sensor head

28   of Fig. 2;

29

30   Fig. 4 is a side view of the sensor head of Fig.

31   2;

32

33   Fig. 5 is a schematic perspective view of an

34   apparatus incorporating the sensor head of Figs. 2

35   to 4;

36

1   Fig. 6 is a perspective view illustrating an

2   alternative form of sensor head;

3

4   Fig. 7 is a schematic end view showing another

5   form of sensor head;

6

7   Figs. 8a and 8b are a cross-sectional side view

8   and a plan view, respectively, of a further sensor

9   head;

10

11   Fig. 9 is a cross-sectional side view of one more

12   embodiment of sensor head;

13

14   Fig. 10 is a perspective view of one type of ear

15   interface apparatus;

16

17   Fig. 11 is a schematic of a multiple laser optical

18   distribution system using lenses, mechanical

19   mounts and a reference detector;

20

21   Fig. 12 is a schematic of a multiple laser optical

22   distribution system using fiber optic cables and a

23   fiber Wavelength Division Multiplexer (WDM), a

24   beam splitter and a reference detector;

25

26   Fig. 13 is a perspective view of a finger

27   interface apparatus with removable inserts that

28   are moulded to fit one individual;

29

30   Fig. 13A shows part of the apparatus of Fig. 13 in

31   greater detail;

32

33   Fig. 14 is a schematic of a semi-spherical

34   detector that contains a hole for the light beam,

35   with a vacuum system and a fiber distribution

36   system;

1

2   Fig. 15 is a perspective view showing one form of

3   the instrument utilizing the vacuum body

4   interface, a semi-spherical detector and the

5   multiple laser source with lenses and mechanical

6   housing;

7

8   Fig. 16 is a perspective view showing one form of

9   the instrument using an ear lobe body interface,

10   with the added feature of being able to manipulate

11   the pressure on the ear lobe; and

12

13   Figs. 17, 18 and 19 are graphs illustrating an

14   example.

15

16   Referring to Fig 1, an important feature of the present

17   invention lies in introducing light energy along an

18   axis into an area of soft tissue and detecting the

19   resulting acoustic response transverse to that axis.

20   Accordingly, in the arrangement of Fig 1A light energy

21   from a diode laser (not shown) is transmitted via a

22   fibre-optic guide 10 to the tip of a finger 12. The

23   photoacoustic interaction occurs in an approximately

24   cylindrical region indicated at 14 from which acoustic

25   energy is radiated in a generally cylindrical manner

26   and is detected by a transversely arranged acoustic

27   transducer 16.

28

29   In Figs 1B and 1C, the principle is similar. The

30   finger 12 is pressed against a support with force F.

31   In Fig 1B, the incident light beam indicated at L is

32   directed as in Fig 1A, and the transducer 16 is at an

33   angle of 45 degrees thereto. In Fig 1B, the angle is

34   90 degrees as in Fig 1A, but the incident beam is

35   directed differently into the fingertip.

36

1   In the present embodiment, the laser wavelength is

2   chosen to achieve high degree of absorption by glucose

3   present in the blood. A suitable wavelength is in the

4   range approximately 1000 to 3000 nm. The laser pulse

5   duration is chosen to be short, typically of the order

6   of 5 to 500 ns, in order to minimise thermal diffusion

7   and thus to optimise the acoustic waveform. For the

8   same reasons, it is desirable to use a spot size which

9   is sufficiently small to minimise thermal diffusion,

10   typically a spot size of the order of 0.05 mm to

11   0.50 mm.

12

13   The efficiency of the photoacoustic detection is also

14   influenced by the positioning and dimensions of the

15   acoustic transducer in relation to the characteristic

16   extinction length of the tissue at the principal

17   wavelengths chosen for measurement. In the fingertip

18   arrangement of Fig. 1, the system efficiency will be

19   improved by optimising the length of the transducer

20   crystal parallel to the axis of the finger, but the

21   length should not be so great as to give rise to

22   undesired signals which would occur at the point of

23   entry of the optical energy into the finger and by

24   reason of interaction of the acoustic energy with bone

25   or other hard tissue.

26

27   A second limit on the size of the acoustic detector

28   derives from the wavelength of the acoustic wave in the

29   tissue. Again making use of Huyghens principal of

30   superposition we view each point of tissue, that is

31   illuminated by the incoming light, as a point source

32   that generates a spherical pressure wave. The signal

33   measured at the detector is just the superposition of

34   all pressure waves from all points that are illuminated

35   by the source light. Normally if the size of the

36   detector is increased then the signal should also

1   increase because more energy is received by the

2   detector. However if the acoustic detector is too

3   large then a pressure wave generated from a tissue

4   element will create a pressure wave that will strike

5   the both ends of the detector. If the paths length

6   from the tissue element to the first end of the

7   detector is different than the path length to the

8   second end of the detector and if this difference in

9   path length is about one half of the acoustic signal

10   wavelength then the signal will destructively interfere

11   with itself and will reduce the magnitude of the

12   measured signal.

13

14   Referring to Fig 2, one manner of carrying out the

15   arrangement shown in Fig 1 makes use of a sensor head

16   having a finger rest 18 which is slidably moveable

17   within housing 20 closed by a front plate 22. The user

18   inserts his finger in a semi-cylindrical depression 24

19   in the finger rest 18 with the finger tip engaged

20   against an end surface 28 which includes an exit face

21   26 of the optical fibre 10. The finger is then pressed

22   downwardly against a resilient bias to enable a

23   standardised contact to be obtained between the skin

24   and the acoustic transducer. The finger tip may first

25   be dipped in water or coated with an aqueous gel to

26   improve the acoustic coupling.

27

28   Referring to Figs 3 and 4, in this preferred

29   arrangement the acoustic transducer comprises a semi-

30   cylindrical piezoelectric transducer 30. The

31   transducer 30 is provided with a backing member 32 of

32   lead or another dense substance, the rear face 34 of

33   which is shaped in irregular curves. The use of the

34   semi-cylindrical transducer 30 maximises the area for

35   reception of acoustic energy from the finger, while the

36   use of a dense backing material minimises ringing

1   effects within the transducer. Additionally, the rear

2   face 34 is shaped as shown to reduce reflection of

3   acoustic energy back towards the piezo crystal.

4

5   Fig 3 also shows the finger rest biased upwardly by the

6   use of constant tension springs 38.

7

8   Fig 5 illustrates schematically the apparatus of Figs.

9   2 and 3 embodied in a self-contained, portable blood

10 monitoring apparatus including a user readout 40. An

11 apparatus of this nature allows a diabetic to monitor

12 blood glucose concentration in a convenient manner, as

13 frequently as may be desired, and in a painless and

14 discreet manner.

15

16 Other forms of photoacoustic sensor head are possible

17 within the scope of the present invention. For

18 example, Fig. 6 shows an arrangement in which a light

19 guide 50 and an acoustic transducer 52 are applied to a

20 finger 54 by means of a hinged clamp member 56. Fig. 7

21 shows a finger 60 engaged by a light guide 62 and an

22 acoustic transducer 64 which are carried on a moveable

23 assembly 66 with the finger 60 being trapped between

24 the moveable assembly 66 and a fixed anvil 68.

25

26 It is also possible to arrange the sensor head to co-

27 operate with a soft tissue surface of the body, for

28 example a soft part of the abdomen. Figs. 8a and 8b

29 show an arrangement in which a cup shaped member 70,

30 suitably of rubber, causes a light guide 72 and an

31 acoustic transducer 74 to be contacted with a bulge of

32 soft tissue 76 which may for example be drawn into

33 contact by means of a partial vacuum within the member

34 70 caused by suction through a conduit 78, or by other

35 mechanical or adhesive means.

36

1   A somewhat similar arrangement is shown in Fig. 9 in

2   which a planar mount 80 carrying a light guide 82 and

3   acoustic transducer 84 is secured to a soft area of

4   body by means of surgical adhesive 86.

5

6   Referring to Fig. 10, one method of performing

7   measurement on an ear lobe involves placing the ear

8   lobe between a fixed plate 87 and a movable plate 88.

9   The acoustic detector 89 is mounted partially

10   perpendicular that is at an acute angle, to the beam

11   axis defined as line going from the center of a lens 90

12   to the center of a window 91. It has been found that

13   the system works satisfactorily with the detector 89 at

14   an angle or 45° to the beam axis. The window 91 and

15   the detector 89 are placed in direct contact with the

16   ear and the opposite plate 88 places pressure on the

17   ear using a suitable mechanism (not shown). This

18   particular embodiment of the ear interface apparatus

19   incorporates an alignment ring 92 which is temporarily

20   attached to the ear and fits over the window housing 91

21   to aid in aligning ear into the same location every

22   time.

23

24   Referring to Fig. 11, one method of combining light

25   sources into the instrument is to use a mechanical

26   housing 93 with several holes used to align lenses 95

27   and laser diodes 94. The housing shown uses a

28   hexagonal array of seven holes. The sources and lenses

29   are arranged in such a way that they all focus to the

30   same location 96 which could be on the surface of the

31   body part. This design does not show the inclusion of

32   beamsplitters and reference detectors but they can be

33   added in an alternative arrangement.

34

35   An alternative method of combining several sources into

36   one beam is shown in Fig. 12. Several laser diodes 97

1   are shown coupled to individual fiber optic cables 131.

2   These cables 132 are combined using a fiber Wavelength

3   Division Multiplexer (WDM) 98. Alternative combination

4   methods exist including couplers and multi-fiber

5   bundles. The combined light exits the WDM 98 in a

6   single fiber 104 and terminates at the focal point of a

7   lens 131. This end of the fiber is imaged to the end

8   of the finger 103 to a spot 102 using another lens 130.

9   Some of the light is split off the main beam using a

10 beam splitter 100 and focused onto a reference detector

11 101 using another lens 99. Additional reference

12 detectors and/or beamsplitters can be added to the

13 distribution system without changing its function.

14 Alternatively a reference detector could look directly

15 at the body part to measure the light reflecting off

16 the surface, as a measure of the overall light energy

17 entering the body part.

18

19 Referring to Fig. 13, another method of using a finger

20 as the body part and including removable inserts is

21 shown. A finger 105 is inserted into an insert 106

22 that is used to customize the finger holder to a

23 particular finger. The moulded insert 106 is placed

24 into a housing 107. The finger 105 is placed against a

25 semi-cylindrical acoustic detector in a module 108 which

26 is also attached to the housing 107. A cover 109 for

27 the housing 107 contains a mechanism 111 to apply

28 constant force to the finger 105. The light beam 110

29 is introduced into the finger 105 using a suitable

30 optical distribution system (not shown). Fig. 13A shows

31 the module 108 in greater detail. A base 200 carries a

32 part-cylindrical piezo transducer 202 on a support 204.

33 206 indicates a coaxial connector to communicate the

34 transducer signal.

35

36 Fig. 14 shows a schematic of an alternative to the

1   vacuum arrangement shown in Figs. 8 and 9. In this
2   system a photoacoustic reader 121 is placed against the
3   skin 113 with a semi-spherical detector 112 in contact
4   with the skin 113. A vacuum pump 115 and vacuum seal
5   116 create a negative pressure and pull the skin 113
6   against the detector 112. Processing electronics 119
7   energizes light sources 118 and an optical distribution
8   system 117 routes the light to the body part through a
9   hole in the top of the semi-spherical detector 112.
10 The optical distribution system 117 directs a small
11 portion of the light to a reference detector 114. The
12 processing electronics 119 measures the signal from the
13 acoustic detector 112 and the reference detector 114
14 for each optical source 119 and calculates the glucose
15 value. The value is displayed on a display 120.
16
17 Fig. 15 shows a similar system 125, only using another
18 type of optical distribution system 127. Again a
19 vacuum pump 123 creates a negative pressure which draws
20 the skin up to an acoustic detector 122. Processing
21 electronics 124 signals light sources in optical
22 distribution system 127 to illuminate and a signal is
23 generated at acoustic detector 122. The processing
24 electronics 124 calculates the proper value and
25 displays it on a display 126.
26
27 Fig. 16 shows an alternative arrangement of a photo-
28 acoustic reader. In this system 128, the vacuum system
29 is replaced with an ear squeeze mechanism 129 which
30 applies pressure to the ear. An acoustic detector 130
31 detects the signals from the ear lobe.
32
33 In the most straightforward forms of the invention, a
34 single analyte such as glucose in blood can be measured
35 by using light of selected wavelengths and by measuring
36 the area or the amplitude of the received acoustic

1   pulse. It is preferable to make each measurement by

2   using a train of pulses, for example about 100 pulses,

3   and averaging the results in order to minimise the

4   effects of noise and pulse effects in the blood flow.

5

6   The accuracy of the detection system is governed, in

7   part, by the Signal to Noise Ratio (SNR) of the system.

8   Variations in the intensity and duration of the light

9   source can cause the acoustic signal to contain

10   variations. A normalization technique, such as taking

11   the ratio of the acoustic signal to the optical signal,

12   can significantly reduce the effect of the source

13   variations, thereby improving the signal to noise ratio

14   of the system. The optical signal can be measured with

15   a reference detector, or several reference detectors,

16   one for each source or one for a wavelength range. An

17   equation describing this type of normalization follows:

18

19   Acoustic Signal

20   Normalized Signal   =   _____

21   Optical Signal

22

23   In some cases the relationship between the optical

24   signal land the acoustic signal changes with wavelength

25   and light intensity. When this is the case the

26   accuracy of the measurement can be further enhanced by

27   determining the energy dependence of the photoacoustic

28   signal. This may be determined by establishing the

29   specific relationship between the photoacoustic signal

30   land the incident energy from a set of measurements and

31   using this relationship to compensate for the non

32   linear response. An equation describing this type of

33   normalization is as follows:

34

35   Acoustic Signal

36   Normalized Signal = _____

1   Scaling Factor *Optical Signal +

2   Offset

3

4   Other normalization methods can also apply. The time

5   interval between the optical pulse and the detection of

6   the acoustic signal may be used to characterise

7   physical properties such as the velocity of sound in

8   the tissue. In addition, in another embodiment of the

9   device the damping of the acoustic oscillations may be

10   used to monitor the elastic properties of the tissue

11   and, in particular, the compressibility. Both of these

12   aspects may be used in the person to person calibration

13   of the photoacoustic response.

14

15   More complex analysis of the received acoustic energy

16   is possible. For example, a time-gating technique may

17   be used to derive measurement at varying depths within

18   the tissue being examined. Alternatively, an array of

19   detectors can be employed to determine the profile of

20   the absorption of the acoustic signal at different

21   depths and locations. This depth profile will change

22   with the absorption coefficient and could be used as

23   additional information to determine the analyte

24   concentration. It is also possible to derive

25   information relating to a number of analytes of

26   interest by more sophisticated analysis of the received

27   acoustic energy wave forms, for example by analysis of

28   the frequency spectrum by Fourier transform or wavelet

29   analysis techniques.

30

31   Alternatively, or in combination with the frequency

32   techniques and multiple detectors, multiple light

33   sources can aid in the determination of the

34   concentration of a number of analytes.

35

36   There are a number of tissue features which may vary

1   from person to person or with in the same person over

2   time which impact the photoacoustic signal observed.

3   To obtain an accurate measurement of a given analyte,

4   such as glucose, it may be helpful to also determine

5   the concentration of other analytes such as haemoglobin

6   which may act as interferants. One approach is to

7   generate several distinct photoacoustic signals using

8   excitation light of several different wavelengths. For

9   example, excitation light of a wavelength of which

10   haemoglobin absorbs strongly but glucose has little if

11   any absorption could be sued to obtain a measure of the

12   haemoglobin concentration with which to normalize the

13   effect of haemoglobin on measurements made on different

14   persons or on the same person at different times.

15   These measurements which are to be normalized might be

16   based on the photoacoustic signal generated by light of

17   a wavelength at which glucose absorbs.

18

19   It is also possible to measure the concentration of

20   such interferants by other means, such as infrared

21   light absorption, and thus normalize or correct the

22   photoacoustic signal representative of the desired

23   analyte for variations in these interferants. Thus,

24   for example, the photoacoustic signal representative of

25   glucose could be corrected for variations in

26   haemoglobin concentration determined by optical

27   absorption techniques such as those taught in US Patent

28   No 5,702,284.

29

30   For the reliable and reproducible determination of

31   glucose a signal to noise ratio of at least 10,000 is

32   recommended. In this regard water is typically present

33   in human tissue of a concentration of about 50 molar

34   while glucose is present at a concentration of about 5

35   millimolar in a normal individual.

36

1   Apparatus and method embodying the present invention

2   have been found to yield accurate and repeatable

3   results. In the case of blood glucose measurement, the

4   clinical range of glucose concentration is

5   approximately 5-10 m mol/l in healthy subjects, and up

6   to 40 m mol/l in diabetics. An analysis based on

7   simple absorption models suggests that the change in

8   photoacoustic signal over this range might be as little

9   as 0.2%. The present invention has been found to

10   provide a change in photoacoustic signal of up to 140%

11   for a change in glucose concentration of 15m mol/l.

12

13   The precise mechanisms involved are not at present

14   fully understood. It is believed, however, that

15   absorption occurs primarily in body plasma and is

16   modified by the presence of glucose, and that this

17   affects beam geometry.

18

19   Example

20

21   The blood glucose levels of three individuals, one

22   normal individual, one type 1 diabetic and one type 2

23   diabetic, were followed over a two hour period

24   following each individual taking about 75 grams of

25   glucose orally in an aqueous solution by both

26   photoacoustics and direct blood measurement. The

27   results are reported in Figures 17, 18 and 19.

28   Photoacoustic measurements were made every five minutes

29   and blood measurements were made very ten minutes. The

30   blood samples were venous blood samples analysed by the

31   standard glucose oxidase method using a Yellow Springs

32   instrument. The error bands for the blood measurements

33   were derived from the literature accompanying the

34   testing instrument while those for the photoacoustic

35   results were based on the averages taken over 1000

36   pulses. The results were obtained from a configuration

1   similar to that illustrated in Figure 1 in which 10 was
2   an end of a 1 km multimode fibre optic cable which was
3   placed against the finger 12. The other end received
4   600 nanosecond pulses of 1040 nanometer light from a Q
5   switched Nd:YAG laser delivering 2,7 micro joules per
6   pulse for each measurement. Raman interactions in the
7   fibre caused the production of light an additional
8   wavelengths as set forth in the following table:

Wavelength in nm	Average pulse energy in microJoules	Pulse width in ns	Approximate bandwidth in nm
1064	2.7	600	4
1120	2.25	500	6
1176	2.0	450	8
1240	1.5	425	12
1308	0.85	400	15
1390	0.3	350	20
1450	0.1	350-	20
1500	0.2	350	20
1550	0.18	360	20

33 The resulting photoacoustic signal was detected by a
34 5mm disc transducer with a lead backing and fed to an
35 amplifier and an oscilloscope. The transducer was
36 generally placed as 16 in Figure 1 but was not

1 precisely parallel to the beam axis; its detection
2 plane was at an angle of about 20 degrees to the beam
3 axis. The photoacoustic signal was evaluated in terms
4 of the difference in voltage signal from the positive
5 peak of the compression to the negative peak of the
6 relaxation of the acoustic pulse.
7
8 The change in photoacoustic response correlated well
9 with the change in blood glucose concentration over the
10 two hour measurement period. A correlation of 0.89 was
11 achieved on samples ranging from 4 to 35 m mol/l.
12
13 Other modifications and improvements may be made to the
14 foregoing embodiments within the scope of the present
15 invention as defined in the claims.
16

CLAIMS

1. A sensor head for use in photoacoustic in vivo
   measurement, comprising a housing shaped to engage
   a selected body part, light transmission means
   terminating in said housing so as to transmit
   light energy from a light source to enter the body
   part along a beam axis, and acoustic transducer
   means mounted in the housing to receive acoustic
   waves generated by photoacoustic interaction
   within the body part, the acoustic transducer
   means being disposed in the housing to receive
   said acoustic wave in a direction of high acoustic
   energy.

2. A sensor head according to claim 1, in which the
   acoustic transducer means is arranged at least
   partially perpendicular to the optical beam axis.

3. A sensor head according to claim 2, for use where
   the selected body part is the distal portion of a
   finger, in which the housing includes a generally
   half-cylindrical depression in which the finger
   may be placed with the light transmission means
   aimed at the end of the finger.

4. A sensor head according to any preceding claim, in
   which the acoustic transducer means comprises a
   piezoelectric transducer which is of a semi-
   cylindrical shape.

5. A sensor head according to any preceding claim, in
   which the acoustic transducer means comprises a
   piezoelectric transducer which is provided with a
   backing of lead or other dense material.

1   6.   A sensor head according to claim 5, in which said

2   backing has a rear surface shaped to minimise

3   internal acoustic reflection.

4

5   7.   A sensor head according to any of claims 1 to 4,

6   in which the transducer means comprises a

7   capacitor-type detector.

8

9   8.   A sensor head according to any of claims 1 to 4,

10   in which the transducer means comprises a

11   piezoelectric transducer arranged generally

12   perpendicular to the optical axis to detect the

13   acoustic wave which is propagating in a direction

14   opposite to the direction of propagation of the

15   light beam.

16

17   9.   A sensor head according to claim 8, in which the

18   transducer is part-spherical with an aperture to

19   allow access for the light beam.

20

21   10. A sensor head according to any preceding claim,

22   including a surface wave detector for

23   characterizing tissue properties.

24

25   11. A sensor head according to any preceding claim,

26   including means for ensuring a consistent contact

27   pressure between a selected body part and the

28   acoustic transducer means.

29

30   12. A sensor head according to claim 11, for use where

31   the selected part is the distal portion of a

32   finger, said means being provided by mounting a

33   portion of the housing engaged by the finger in a

34   resiliently biased fashion against the remainder

35   of the housing, and providing means to ensure that

36   measurement is effected when a predetermined force

1   or pressure is applied by the subject against the

2   resilient bias.

3

4   13. A sensor head according to claim 11, for use where

5   the selected part is the earlobe, said means being

6   provided by two plates, between which the earlobe

7   may be placed, and means for pressing the plates

8   together to apply pressure to the ear.

9

10   14. A sensor head for use in photoacoustic in-vivo

11   measurements, comprising a housing shaped to

12   receive a removable insert; a removable insert

13   that engages a selected body part, the insert

14   being fitted to an individual, allowing for a

15   range of sizes of body parts to be used; light

16   transmission means terminating in or near said

17   removable insert so as to transmit light energy

18   from a light source to enter the body part along a

19   beam axis; and an acoustic transducer means

20   mounted in the housing or in the removable insert

21   to receive acoustic waves generated by

22   photoacoustic interaction within the body part,

23   the acoustic transducer means being disposed in

24   the housing or insert to receive said acoustic

25   waves in a direction of high acoustic energy.

26

27   15. An in-vivo measuring system comprising in

28   combination: a sensor head as claimed in any

29   preceding claim; a light source coupled with the

30   light transmission means; and signal processing

31   means connected to receive the output of the

32   acoustic transducer means and to derive therefrom

33   a measurement of a selected physiological

34   parameter.

35

36   16. The system of claim 15, in which the light

1   transmission means is a fiber optic distribution
2   system.

3

4 17. The system of claim 16, in which there is a
5   plurality of light sources each connected to an
6   individual fiber and the respective fibers are
7   joined by a wavelength division multiplexer or a
8   fiber coupler.

9

10 18. The system of claim 16 or claim 17, in which the
11   fiber optic distribution system terminates in
12   contact with the body part.

13

14 19. The system of claim 16 or claim 17, in which the
15   fiber optic distribution system communicates with
16   the body part via optical elements such as lenses
17   and beamsplitters.

18

19 20. The system of claim 15, in which the light
20   transmission means comprises optical elements
21   mounted in mechanical holders and arranged to
22   convey the light from the light source to a
23   location in proximity to the body part.

24

25 21. The system of claim 19 or claim 20, in which the
26   light transmission means includes at least one
27   beamsplitter arranged in the light path to direct
28   a portion of the light to a respective reference
29   detector to measure the energy of the light
30   entering the body part.

31

32 22. The system of any of claims 15 to 21, in which the
33   signal processing means is adapted to perform a
34   multi-dimensional processing method.

35

36 23. The system of claim 22, in which the signal

1   processing means is adapted to perform one of

2   Classical Least Squares or Partial Least Squares.

3

4

5   24.   The system of any of claims 15 to 21, in which the

6   signal processing means comprises a Neural

7   Network.

8

9

10   25.   The system of any of claims 15 to 24, in which the

11   signal processing means is operable to analyse the

12   signals for their frequency content using one of

13   Fourier Analysis and Frequency Filtering.

14

15   26.   The system of any of claims 15 to 25, in which the

16   signal processing means additionally applies

17   techniques that use time information.

18

19   27.   The system of claim 26, in which the time

20   information processed is the time delay from

21   source trigger.

22

23   28.   The system of any of claims 15 to 25, in which the

24   signal processing means additionally applies

25   techniques that combine both frequency and time

26   information.

27

28   29   The system of claim 28, in which the signal

29   processing means performs wavelet analysis.

30

31   30.   The system of any of claims 15 to 29, in which the

32   light source is a laser light source.

33

34   31.   The system of claim 30, in which said laser light

35   source is selected from a pulsed diode laser, a

36   set of pulsed diode lasers, and a tunable laser

1   source.

2

3   32. The system of claim 31, for use in measuring blood

4   glucose concentration, in which the light source

5   is a laser diode with a wavelength in the range of

6   approximately 600 nm to 10,000 nm and a pulse

7   duration of the order of 5 to 500 ns.

8

9   33 The system of any of claims 30 to 32, in which the

10   light transmission means is arranged to produce a

11   spot size of the order of 0.05 mm to 0.50 mm.

12

13   34. The system of any of claims 15 to 29, in which

14   there are multiple light sources and means are

15   provided for time multiplexing the multiple

16   sources such that: each source is switched on and

17   generates an optical pulse, or a set of optical

18   pulses, the pulse, or set of pulses, generates an

19   acoustic signal that is detected by the detector,

20   and each source is pulsed in sequence until all

21   sources have been used to generate their own

22   signals.

23

24   35. The measuring system of any of claims 15 to 34, in

25   the form of a self contained system including a

26   power supply and a readout, which may be carried

27   on the person and used at any convenient time.

28

29   36. The system of claim 35, including facilities for

30   connection to a cellular telephone, two-way pager

31   or other communication device for routine

32   transmission of measurements taken to a central

33   data collection point.

34

35   37. The system of any of claims 15 to 36, further

36   including means for manipulating the body part

1   under measurement and for performing additional

2   measurement of the tissue to obtain other

3   information about the state of the physiology of

4   the issue.

5

6   38. The system of claim 37, in which said manipulating

7   means includes means for squeezing a body part,

8   such as an earlobe, and means for making photo

9   acoustic measurements at several different

10   pressures.

11

12   39. The system of claim 37 or claim 36, including

13   temperature measurement means for measuring the

14   temperature of the body site, and in which the

15   signal processing means is arranged to apply a

16   correction to the measurements based upon the

17   temperature of the body site.

18

19   40. The system of claim 39, further including means

20   for inducing temperatures above and below ambient

21   in the body part.

22

23   41. The system of any of claims 15 to 40, comprising a

24   means for storing one or both of calibration

25   coefficients and operational parameters in order

26   to calibrate the instrument and to set critical

27   operational parameters.

28

29   42. The system of claim 41, in which the signal

30   processing means is operable to adjust the

31   calibration coefficients and operational

32   parameters to be specific to a particular person.

33

34   43. The system of claim 42, when dependent upon claim

35   14, in which the calibration coefficients and

36   operational parameters specific to a particular

1   person are contained in a storage site located in

2   the removable insert.

3

4   44.   The system of claim 43, in which additionally

5   calibration coefficients and operational

6   parameters specific to the reader system are

7   stored in the non-removable housing.

8

9   45.   The measuring system of any of claims 15 to 44,

10   further including connection means for connecting

11   the measuring system to an invasive measuring

12   system for the purpose of calibrating or adjusting

13   the operational parameters of the non-invasive

14   measuring system.

15

16   46.   The system of claim 45, in which the connection

17   means is selected from a cable link, IR link or

18   radio waves.

19

20   47.   A method of operating a measurement system as

21   claimed in claim 34 to remove instrument drift

22   from the measurement, the method comprising the

23   steps of:

24

25   1)   placing a calibration standard in the reader

26   in place of the body part;

27

28   2)   measuring the signal from the standard for

29   each wavelength and storing the values in the

30   calibration storage location;

31

32   3)   before making a measurement of a body part,

33   placing the calibration standard in the

34   reader;

35

36   4)   measuring the signal from the standard for

each source;

5) comparing the just measured standard values
to the stored calibration values;

6) calculating correction factors for each
source wavelength.

7) removing the standard and placing the body
part in the reader;

8) measuring the signal from the body part for
each source; and

9) adjusting the measured values using the
calculated correction factors.

48. The method of claim 47, in which a further
correction factor is calculated for the instrument
temperature.

49 A method of measuring a biological parameter in a
subject, the method comprising the steps of:

directing one or more pulses of optical
energy from the exterior into the tissue of a
subject along a beam axis, the optical energy
having a wavelength selected to be absorbed
by tissue components of interest, thereby to
produce a photoacoustic interaction;

detecting acoustic energy resulting from said
photoacoustic reaction by means of a
transducer positioned to intercept acoustic
energy propagating in a direction other than
the forward direction of said beam axis; and

1   deriving from said detected acoustic energy a

2   measure of the parameter of interest.

3

4 50   The method of claim 49, in which the parameter of

5   interest is blood glucose, and the optical energy

6   has a wavelength in the range of approximately 600

7   mm to 10,000 mm and a pulse duration of the order

8   of 5 to 500 ms.

9

10 51   The method of claim 49 or claim 50, in which a

11   train of pulses is applied and the detected

12   signals are averaged to derive said measure.

13

14 52   The method of any of claims 49 to 51, in which

15   said measure is derived from the energy of the

16   detected signal.

17

18 53   The method of any of claims 49 to 52, in which the

19   optical energy is directed into a body part which

20   is substantially composed of soft tissue and free

21   of bone.

22

23 54   Apparatus for measuring a biological parameter in

24   a subject, the apparatus comprising:

25

26   means for directing one or more pulses of optical

27   energy from the exterior into the tissue of a

28   subject along a beam axis, the optical energy

29   having a wavelength selected to be absorbed by

30   tissue components of interest, thereby to produce

31   a photoacoustic interaction;

32

33   transducer means arranged to detect acoustic

34   energy resulting from said photoacoustic reaction

35   by intercepting acoustic energy propagating in a

36   direction other than the forward direction of said

beam axis; and

means for deriving from said detected acoustic
energy a measure of the parameter of interest.

55 Apparatus according to claim 54, in which said
directing means incudes means for receiving a
selected body part such that the optical energy is
directed into a portion of the subject's body
which is substantially free of bone.

56 A method of correcting measurement of an analyte
based on a photoacoustic signal obtained from a
living being comprising determining the
concentration of other constituents in the being
which have a significant effect on the
photoacoustic signal and tend to vary from
individual to individual or over time, and
adjusting the measurement to remove the effect of
variations in the concentrations of said other
constituents.

57 The method of claim 56 in which the analyte is
glucose.

58 The method of claim 57 in which the concentration
of haemoglobin is determined and used to adjust
the measurement.

59 A method of establishing a photoacoustic signal
obtained from a living being comprising using the
ratio of the acoustic signal obtained to the
optical signal which generated the acoustic signal
to determine the concentration of an analyte
present in said being.

1   60   The method of claim 59 in which the analyte is
2   glucose.
3
4   61   A method of normalizing a photoacoustic signal
5   obtained from directing an optical beam on the
6   tissue of a living being comprising determining
7   the dependence of the photoacoustic signal on the
8   energy of the optical beam from a series of
9   measurements at different energies for the type of
10   tissue involved.
11
12
13